

Referring now to United States Patent No. 5,288,507 hereinafter referred to as Sims, there is taught a combination of an anti-inflammatory and particularly (S)-ibuprofen being substantially free of the (R)-ibuprofen isomer, plus in one alternative embodiment it is mentioned at column 4, line 61 onward that an antiulcerative agent might be used such as misoprostol or the like. The invention may take the form of tablets and the active may be admixed with pharmaceutically acceptable diluents such as lactose, starch, sucrose, and a host of other items listed at column 5, line 5 onwards. There is however, no discussion within the Sims reference to provide the invention as defined in Applicant's claim 1.

*A pharmaceutical tablet comprising a shell in which is imbedded two smaller tablets covered by the material of the shell of the pharmaceutical tablet, one of which smaller tablets comprises an NSAID and the other of which smaller tablets comprises misoprostol, whereby the two smaller tablets are not exposed to the environment at the surface of the pharmaceutical tablet, being protected by said shell.*

There is no discussion within Sims of a pharmaceutical tablet which includes a shell in which is embedded two smaller tablets, one of which is an NSAID and one of which is misoprostol. There is no motivation within Sims to do so, and clearly with the Examiner's own admission in the action dated March 4, 2002, there is apparently no teaching in the direction of Applicant's claim 1, otherwise the Examiner would have stated such.

Referring now to Kararli, United States Patent No. 5,935,939 there is taught a stabilized dispersion of misoprostol using amorphous excipients resulting in a stable solid state amorphous dispersion of misoprostol and the excipient. Fundamentally therefore, the Kararli patent teaches a need to stabilize a misoprostol, in that prostaglandins are difficult to formulate into stable pharmaceutical dosage forms because of their relative instability. The '939 patent therefore has added to the state of the art, one way of stabilizing the misoprostol. Clearly there is nothing within

Kararli other than the fact that the dispersions can be used in the production of tablets as in Example 1 wherein they are ground using a mortar and pestle and then milled. But Kararli is silent with regard to how the dispersion might be utilized in tablet form other than that it may be utilized in a tablet form.

However, there is nothing within Kararli that teaches anything but a stable solid state amorphous dispersion of mistoprostol with an excipient selected from a certain group of excipients as set out in Claim 1. There is clearly nothing within the Kararli reference that teaches Applicant's invention as specified in Claim 1 as follows.

*A pharmaceutical tablet comprising a shell in which is imbedded two smaller tablets covered by the material of the shell of the pharmaceutical tablet, one of which smaller tablets comprises an NSAID and the other of which smaller tablets comprises misoprostol, whereby the two smaller tablets are not exposed to the environment at the surface of the pharmaceutical tablet, being protected by said shell.*

Referring now to United States Patent No. 5,523,321 to Stuerzebecher there is taught combination products containing a prostaglandin and a thromboxane receptor antagonist suitable for joint application to thrombotic and thromboembolic syndromes.

This patent therefore is silent with regard to the use of NSAIDs; it is further silent with regard to the use of mistoprostol. The primary problem being dealt with in the '321 patent is coronary heart diseases, coronary thrombosis, or the like as listed at column 1, lines 17 onward, for the inhibition of blood platelet aggregation. The combination product when given orally, may be in the form of a tablet which can be produced in "the usual way" as stated at column 4, line 34; and column 4, line 53.

Page 5

Referring now to Example 1, clearly the components 3, 4 and 5 are sifted, mixed and granulated with the solution of item 1 in example 1 which is Iloprost in 50% ethanol. The term granulating therefore, clearly refers to wet granulating and that is to say the formation of granules from particles of items 3, 4 and 5; lactose, cornstarch and polyvinylpyrrolidone 2500 which granules are subsequently dried and mixed with items 2 and 6 prior to molding into rounded tablets. Clearly, granules are therefore produced. However, respectfully the Examiner has misread the term in concluding that granules render tablets obvious. In fact, granules are an intermediate step prior to a tableting process.

As support of what a man skilled in the art would know about granulation, Applicant encloses herewith pages 616 to 628 of *"Pharmaceutics: The Science of Dosage Form Design"*, published by Churchill Livingstone. The Examiner is referred to the entire section, and particularly that granules may be mixed with other excipients prior to tablet compression. Granules may be formed by the dry granulation method or the wet granulation method. The '321 patent clearly refers in the examples only to wet granulation. As can be seen from reading the section provided from the Churchill Livingstone reference, (which is not an extensive reference manual on granulation), granulation is not by any means a simple process and must be monitored at all times to prevent aggregation of the granules to sizes beyond that which is desired. Clearly, there is nothing within the teachings of Churchill Livingstone that agrees in any way with the Examiner's conclusion that allegedly granules would render obvious the use of tablets. Applicant does not believe that a man skilled in the art would arrive at such a conclusion, only that granules are be formed by wet granulation methods which are left unspecified in example 1 of the '321 patent. As per the teachings of Churchill Livingstone granules may be provided by wet or dry granulation in various processes and are a precursor to tableting or to be used in dosage forms when gelatin capsules are being filled to

Page 6

form granules of predetermined size and configuration filled into these gelatin capsules.

Referring to the McGraw-Hill DICTIONARY OF SCIENTIFIC AND TECHNICAL TERMS (Fourth edition) also attached for the Examiner's information,

Tableting is defined as follows: a punch-and-die procedure for compaction of powdered or granular solids; used for pharmaceuticals, food products, fireworks, vitamins, and dyes.

Granulate is defined as follows: to form or crystallize into grains, granules, or small masses.

Clearly, with respect, the Examiner has misread example 1 of the '321 patent and incorrectly concluded that the resulting granules of the granulating step of example 1 would "make the use of tablets in the instant invention obvious" when '321 is silent on the specifications of the granules as per Churchill Livingstone. Clearly the process used in example 1 of '321 is not specified. It is therefore unlikely that a man skilled in the art would reach such a conclusion. Clearly the Examiner is relying on 20/20 hindsight which is forbidden.

In Re: Fritch, 23 U.S.P.Q. 2d 1780 (Fed. Cir. 1992)

"Wilson and Hendrix fail to suggest any motivation for, or desirability of, the changes espoused by the Examiner and endorsed by the Board. Here, the Examiner relied upon hindsight to arrive at the determination of obviousness. It is impermissible to use the claimed invention as an instruction manual or "template" to piece together the teachings of the prior art so that the claimed invention is rendered obvious (emphasis added). The court has previously stated that "[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."

There is nothing within the teachings of the '321 patent that would motivate one skilled in the art to somehow combine the teachings of Sims and Kararli with '321 since the problems being solved by each reference are somewhat mutually exclusive. Kararli teaches only a stabilized dispersion of misoprostol using amorphous excipients resulting in a stable solid state amorphous dispersion of misoprostol and the excipient. Sims teaches a combination of an anti-inflammatory and particularly (S)-ibuprofen being substantially free of the (R)-ibuprofen isomer, plus in one alternative embodiment an antiulcerative agent might be used such as misoprostol or the like. '321 teaches combination products containing in one embodiment a prostaglandin and a thromboxane receptor antagonist suitable for joint application to thrombotic and thromboembolic syndromes. How then would one skilled in the art of Sims be motivated to use the amorphous form of misoprostol of Kararli and even if they were; with no admission that this is the case, why would such a combination be further combined with the teachings of '321 when clearly the problems addressed in '321 are quite different; namely cardiac and cardiovascular problems. What would motivate one skilled in the art to do so. Clearly the Examiner is incorrectly picking and choosing from the prior art elements in creating a 20/20 hindsight reconstruction.

*ATD Corporation v. Lydall, Inc.*, 48 USPQ 2d 1321, 1329 (Fed. Cir. 1998)

Determination of obviousness can not be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention. **There must be a teaching or suggestion within the prior art, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources of information, to select particular elements, and to combine them in the way they were combined by the inventor.**(emphasis added)

Nothing within the Examiner's purported combination of Sims, Kararli and '321 reference teaches Applicant's invention as set out in Claim 1. The combination falls well short and at best, if made, might include, if the Examiner's logic were used (with no admission being made that such logic is acceptable in law or correct),

granules of an active which may be a prostaglandin and an NSAID. However such a combination falls well short of Applicant's invention namely:

*A pharmaceutical tablet comprising a shell in which is imbedded two smaller tablets covered by the material of the shell of the pharmaceutical tablet, one of which smaller tablets comprises an NSAID and the other of which smaller tablets comprises misoprostol, whereby the two smaller tablets are not exposed to the environment at the surface of the pharmaceutical tablet, being protected by said shell.*

If one skilled in the art were to combine the teachings of Sims, the '321 reference and Kararli they would not arrive at Applicant's invention. First of all, there is nothing within the '321 reference that teaches the use of two separate tablets and as taught in Applicant's disclosure that either by using dry powder or granules the two smaller tablets are formed, one containing an NSAID and the other containing misoprostol. Clearly, there is no teaching in any of the references alone and in combination to do so. Respectfully, the Examiner has relied a 20/20 hindsight using the Applicant's invention as a blueprint hoping to arrive at such a combination but has respectfully fallen well short, since clearly there is no teaching within either of the three references with respect to Applicant's invention as set out in Claim 1 above, and there is no motivation from either of the references alone or in combination to arrive at Applicant's invention. The Examiner however, has incorrectly concluded that the combination is allegedly relevant having misread Stuerzebecher resulting in firstly misreading, and then misapplying the term granules from a very limited disclosure in the examples, and particularly Example 1 of Stuerzebecher. One granulates prior to tableting in many cases depending on the disintegration and release characteristics desired. How then does the Examiner reach the conclusion that Claim 1 is obvious. Clearly, this is a 20/20 hindsight reconstruction, that is to say using the term granules to render allegedly obvious the term tablets and even if this were the case, there still is no teaching in any of the

three references, Sims, Stuerzebecher or Kararli alone or in combination that teaches Claim 1 as set out below.

*A pharmaceutical tablet comprising a shell in which is imbedded two smaller tablets covered by the material of the shell of the pharmaceutical tablet, one of which smaller tablets comprises an NSAID and the other of which smaller tablets comprises misoprostol, whereby the two smaller tablets are not exposed to the environment at the surface of the pharmaceutical tablet, being protected by said shell.*

Respectfully, the Examiner is creating a 20/20 hindsight reconstruction using Applicant's invention as a blue print to allegedly find elements of Applicant's combination in the prior art. This is not permissible as set out In Re: Rouffet, 47 U.S.P.Q. 2d 1453 (Fed. Cir. 1998)

*To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed. (emphasis added)*

The following cases also review the Federal Circuits recent decisions regarding hindsight reconstruction.

*In re Oetiker*, 24 USPQ 2d 1443, 1446 (Fed. Cir. 1992)

The combination of elements from non-analogous sources, in a manner that reconstructs the applicant's invention only with the benefit of hindsight, is insufficient to present a prima facie case of obviousness. **There must be some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the field of the invention would make the combination. (emphasis added)** That knowledge can not come from the applicant's invention itself.

*ATD Corporation v. Lydall, Inc.*, 48 USPQ 2d 1321, 1329 (Fed. Cir. 1998)

Determination of obviousness can not be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention. **There must be a teaching or suggestion within the prior art, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources of information, to select particular elements, and to combine them in the way they were combined by the inventor. (emphasis added)**

*Al-Site Corp. v. VSI Int'l, Inc.*, 50 USPQ 2d 1161, 1171 (Fed. Cir. 1999)

VSI is unable, however, to point to any specific teaching or suggestion for making this combination. VSI instead relies on what it presumes is the level of knowledge of one of ordinary skill in the art at the time of the invention to supply the missing suggestion to combine. In the first place, the level of skill in the art is a prism or lens through which a judge or jury views the prior art and the claimed invention. This reference point prevents these deciders from using their own insight or, worse yet, hindsight, to gauge obviousness. **Rarely, however, will the skill in the art component operate to supply missing knowledge or prior art to reach an obviousness judgment. . . . Skill in the art does not act as a bridge over gaps in substantive presentation of an obviousness case** (emphasis added), but instead supplies the primary guarantee of objectivity in the process.

*In re Dembiczak*, 50 USPQ 2d 1614, 1616-17 (Fed. Cir. 1999) (quotations omitted)

Our analysis begins in the text of section 103 quoted above, with the phrase "at the time the invention was made." For it is this phrase that guards against entry into the tempting but forbidden zone of hindsight, . . . when analyzing the patentability of claims pursuant to that section. Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, **guided only by the prior art references and the then-accepted wisdom in the field.** . . . (emphasis added) Close adherence to this methodology is especially important in the case of less technologically complex inventions, where the very ease with which the invention can be understood may prompt one to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher. . . . In this case, the Board fell into the hindsight trap. . . . The range of sources available, however, does not diminish the requirement for actual evidence. That is, **the showing must be clear and particular** (emphasis added).

Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references.

*In Re: Fritch*, 23 U.S.P.Q. 2d 1780 (Fed. Cir. 1992)

"Wilson and Hendrix fail to suggest any motivation for, or desirability of, the changes espoused by the Examiner and endorsed by the Board. Here, the Examiner relied upon hindsight to arrive at the determination of obviousness. It is impermissible to use the claimed invention as an instruction manual or "template" to piece together the teachings of the prior art so that the claimed invention is rendered obvious (emphasis added). The court has previously stated that "[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."

*In Re: Rouffet*, 47 U.S.P.Q. 2d 1453 (Fed. Cir. 1998)

"As this court has stated, "virtually all [inventions] are combinations of old elements." *Environmental Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 698, 218 USPQ 865, 870 (Fed. Cir. 1983); see also *Richdel, Inc. v. Sunspool Corp.*, 714 F.2d 1573, 1579-80, 219 USPQ 8, 12 (Fed. Cir. 1983) ("Most, if not all,



*inventions are combinations and mostly of old elements." ). Therefore an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be "an illogical and inappropriate process by which to determine patentability." *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570, 38 USPQ 2d 1551, 1554 (Fed. Cir. 1996).*

*To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed. (emphasis added)*

*This court has identified three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art. In this case, the Board relied upon none of these. Rather, just as it relied on this high level of skill in the art to overcome the differences between the claimed invention and the selected elements in the references, it relied upon the high level of skill in the art to provide the necessary motivation. The Board did not, however, explain what specific understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested the combination. Instead, the Board merely invoked the high level of skill in the field of art. If such a rote invocation could suffice to supply a motivation to combine, the more sophisticated scientific fields would rarely, if ever, experience a patentable technical advance. Instead, in complex scientific fields, the Board could routinely identify the prior art elements in an application, invoke the lofty level of skill, and rest its case for rejection. To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness.*

*Because the Board did not explain the specific understanding or principle within the knowledge of a skilled artisan that would motivate one with no knowledge of Rouffet's invention to make the combination, this court infers that the examiner selected these references with the assistance of hindsight. This court forbids the use of hindsight in the selection of references that comprise the case of obviousness. (emphasis added) See In re Gorman, 933 F.2d 982, 986, 18 USPQ 2d 1885, 1888 (Fed. Cir. 1991). Lacking a motivation to combine references, the Board did not show a proper prima facie case of obviousness. This court reverses the rejection over the combination of King, Rosen and Ruddy."*

Referring now to United States Patent No. 5,232,704 to Franz, herein referred to as '704 there is clearly taught that prostaglandins are involved in the treatment of ulcers. They inhibit gastric secretions from the stomach parietal. The '704 reference

therefore proposes to provide a bi-layer floating dosage form to improve the delivery of the prostaglandin and particularly misoprostol to a patient. The '704 reference then goes on in the background to discuss other buoyant type floating tablets, and further in the summary of the invention clearly teaches a non-compressed bi-layer formulation, wherein one layer includes the drug release layer, and where the other is only the buoyant or floating layer, in order to ensure that substantially all of the drug is released in the stomach over the extended period of time. Gelling agents therefore are incorporated in the buoyant layer which hydrates in gastric juices and forms a gelatinous barrier or mass which is contained in a separate layer from the drug release formulation layer. This theme is repeated throughout the detailed description of the '704 specification, and at column 4, line 4, it states,

*"Examples of suitable NSAID's to mix or combine with a prostaglandin drug are diclofenac, piroxicam, ibuprofen or naproxen. An example of a suitable combination or mixture is diclofenac in a therapeutic amount such as from about 25 to 75 milligrams and the prostaglandin misoprostol in a therapeutic amount of from about 100 to 200 micrograms."*

Clearly, it was the intent of the '704 Franz teaching that the drugs are mixed and combined in the one drug layer and never in the buoyant layer. Clearly, Gimet the '225 reference teaches that this should not be done, and that a problem will result in doing so. It is never contemplated within Franz to separate these two components since Franz did not appreciate the problem identified in the later reference Gimet '225 and addressed by Applicants invention in claim 1. Franz was preoccupied with floatation and to ensure that the composition is buoyant in the stomach and remains in the stomach for the full period that the NSAID is being ingested. The Examiner is encouraged to re-read the specification of Franz to arrive at the conclusion and the only conclusion available, that is to say the second layer is

the buoyancy layer designed for particular residence time of the composition within the stomach to ensure that the entire contents of the composition is ingested in the stomach.

In the preferred embodiment of Franz the drug release layer is filled into a capsule without any compaction using a conventional capsule filling machine and the buoyant layer is then added by free-flowing the powder mixture into the capsule body. An over-filling of the buoyant layer is used to minimize mixing of the two layers. It is further recommended that the composition be taken after ingesting a heavy meal which in turn would ensure the buoyancy or floatation of the composition in the contents of the stomach.

Clearly therefore, Franz does not even fully appreciate the problems associated with combining NSAID's and misoprostol since Franz teaches mixing of the NSAID and the prostaglandin in one layer. A man skilled in the art would not therefore follow such teaching to provide a composition containing NSAID's and misoprostol in the same layer. Surely a fair objective reading of Franz would not result in Applicant's invention, namely:

*A pharmaceutical tablet comprising a shell in which is imbedded two smaller tablets covered by the material of the shell of the pharmaceutical tablet, one of which smaller tablets comprises an NSAID and the other of which smaller tablets comprises misoprostol, whereby the two smaller tablets are not exposed to the environment at the surface of the pharmaceutical tablet, being protected by said shell.*

Clearly, Franz does not teach two tablets contained within a pharmaceutical tablet including a shell which surrounds the two smaller tablets each containing only

one of the NSAID and the misoprostol. Franz never appreciated the fact that the prostaglandin and an NSAID should not be mixed together in the same layer. He provides a second buoyant layer as admitted by the Examiner in order to provide full ingestion of the actives within the stomach.

Clearly, however, Franz did not even appreciate the need of separating the NSAID and the misoprostol as set out in Applicant's invention as follows:

*A pharmaceutical tablet comprising a shell in which is imbedded two smaller tablets covered by the material of the shell of the pharmaceutical tablet, one of which smaller tablets comprises an NSAID and the other of which smaller tablets comprises misoprostol, whereby the two smaller tablets are not exposed to the environment at the surface of the pharmaceutical tablet, being protected by said shell. (emphasis added)*

Referring now to any combination of Franz and Stuerzebecher '321 patent, Franz does not address the problems as set out in Applicant's disclosure, that is to say the importance of protecting misoprostol from the environment and from the NSAID separately. Clearly, the Examiner has also stated that "Franz does not disclose that the NSAID and misoprostol used are tablets.". Applicant presumes the Examiner means that Franz does not disclose that the NSAID and misoprostol used are used as separate tablets. Applicant agrees. Franz teaches that all of the drug in the composition is in the drug release layer.

But The Examiner has, respectfully again, as with the prior rejection of Sims, in view of Kararli in further view of '321, misapplied and misread Stuerzebecher teachings with regard to the term "granule" as rendering the term "tablet" obvious to one skilled in the art for the same reasons set out above. This is simply not the case. Even if the Examiner's alleged combination were made, respectfully there would not be two smaller tablets in a pharmaceutical tablet since at best '321 teaches a prostaglandin and a thromboxane receptor antagonist suitable for joint application to thrombotic and thromboembolic syndromes, meaning simultaneous but separate administration or combined in a dose unit. In this regard please see column 2 line 31 to 35 of '321. Since neither Franz nor '321 teach two separate smaller tablets in a pharmaceutical tablet even if the term "granules" were read in the manner alleged by the Examiner, and for the reasons set out above this is clearly not the case, one would still not arrive at Applicant's teaching and Claim 1 as follows:

*A pharmaceutical tablet comprising a shell in which is imbedded two smaller tablets covered by the material of the shell of the pharmaceutical tablet, one of which smaller tablets comprises an NSAID and the other of which smaller tablets comprises misoprostol, whereby the two smaller tablets are not exposed to the environment at the surface of the pharmaceutical tablet, being protected by said shell.(emphasis added)*

Again respectfully the Examiner is attempting to create a 20/20 hindsight reconstruction but has fallen well short in doing so.

In Re: Fritch, 23 U.S.P.Q. 2d 1780 (Fed. Cir. 1992)

"Wilson and Hendrix fail to suggest any motivation for, or desirability of, the changes espoused by the Examiner and endorsed by the Board.

Here, the Examiner relied upon hindsight to arrive at the determination of obviousness. It is impermissible to use the claimed invention as an instruction manual or "template" to piece together the teachings of the prior art so that the claimed invention is rendered obvious(emphasis added). The court has previously stated that "[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."

In Re: Rouffet, 47 U.S.P.Q. 2d 1453 (Fed. Cir. 1998)

*To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed. (emphasis added)*

Referring to the traditional test in Graham and John Deere, Applicant has assessed the scope and content of the prior art cited by the Examiner and set out the differences between the prior art and the claims at issue. Clearly, none of the prior art references alone or in any combination addresses the problem of environmental degradation of the prostaglandin as does Applicant's invention in the manner as contained in amended claim 1. Claim 1-11 are therefore patentable in view of the fact that the specific combination set out above in amended claim 1 is not disclosed in the prior art and is not obvious to one of ordinary skill in the art from the teachings the prior art cited by the Examiner.

Referring to the In Re Sernaker Decision before the Court of Appeals, Federal Circuit 702 F 2d 989, 217 USPQ 1 it was stated therein;

"When one skilled in the art at the time of the invention is considering all the prior art in combination, we wholly fail to perceive what more he would have found. The most that would have appeared to have been suggested was the use of transfer prints on rough substrates by which, no doubt, a variety of designs might have been achieved. Mating or

registering are suggested nowhere in the prior art. Therefore, it does not show how to approach the results this inventor achieved. No prior art suggests expressly or by implication keeping the print off the substrate and providing a "sculptured" embroidery in a pattern to mate and register with the print."...

"The lesson of this case appears to be that prior art references in combination do not make an invention obvious unless something in the prior art references would suggest the advantage to be derived from combining their teachings. It does not appear from the opinion that the inventor actually did anything not disclosed somewhere in the prior art references, and in that regard the case was less favorable for unobviousness than the case at bar, where none of the prior art references disclosed an embroidery inserted between the print and the substrate, "registered" or mated the print with the embroidery, not the substrate, and transferred the print to the insert, not to the substrate."

Following the Re: Sernacker reasoning as well, Applicant's invention is not suggested directly or indirectly from any combination of the prior art since the prior art does not teach that the prostaglandin be contained in a smaller tablet and that the NSAID be contained in a smaller tablet; and both tablets subsequently being contained in a pharmaceutical tablet. The advantages of doing so for the prostaglandin and the NSAID is that the degradation issues set out in the background of Applicant's invention, and in Gimet are clearly addressed by Applicant's improved pharmaceutical tablet heretofore left unaddressed in their entirety by Franz and '321 or Sims, Kararli and '321 and in any combination thereof. Applicant's invention therefore achieves more than any combination of the prior art cited by the Examiner and is clearly patentable. There is no motivation within any of the cited references, absent Applicant's invention and the teaching thereof, to arrive at Applicant's combination. In fact, Applicant submits that Franz and '321 or Sims, Kararli and '321 could not easily be combined and they are to a certain degree mutually exclusive since they in fact teach in opposite directions with respect to the provision of the misoprostol and the NSAID being in one layer in one case, that is

Franz, or '321. Clearly, there is no suggestion therefore in either reference that the compositions could be combined in the manner alleged by the Examiner. The prior art does not suggest the desirability of making such a combination. There is no motivation in the prior art to do so.

The Examiner is referred to in Re: Regal in this regard wherein it states,

*"There must be some logical reason apparent from positive concrete evidence of record which justifies a combination of primary and secondary references."*

Clearly therefore, Applicant has amended the claims to overcome the Examiner's alleged obviousness rejections and it is requested that full reconsideration be given to the claim amendments and Applicant's arguments.

One of the benefits of Applicant's invention is that it overcomes the problem that misoprostol is highly unstable and it is thus desirable not to have the misoprostol and the NSAID mixed together so as to prevent any deleterious effect of the NSAID on the stability of the misoprostol. Applicant refers to the Gimet patent, U.S. Patent 5,601,843, at page 2, line 5 of the Disclosure as one solution. Applicant states however that the difficulty with Gimet is that the misoprostol is disbursed throughout the mantle and is thus exposed to the environment of the surface of the tablet. This exposure increases the vulnerability of the misoprostol to degradation due to the effects of light or atmospheric oxygen and moisture.

In view of the above submissions neither Franz in view of '321 nor Sims, in view of Kararli in further view of '321 teach Applicant's invention and further that



Page 19

no combination nor any one of the references teaches Applicant's invention as set out in claim 1 above.

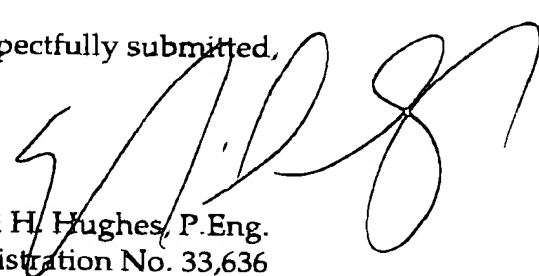
Attached hereto as **Exhibit A** is a marked-up version of the changes made to the claims by the present amendment. Exhibit A is entitled "EXHIBIT A - CLAIMS WITH MARKINGS TO SHOW CHANGES".

Attached hereto as **Exhibit B** is a clean set of all pending claims following entry of this amendment. Exhibit B is entitled: "EXHIBIT B - CLEAN SET OF ALL PENDING CLAIMS FOLLOWING ENTRY OF THE PRESENT AMENDMENT". All of the currently pending claims are consolidated in this list for the convenience of the Examiner.

In view of the above submissions, Applicant respectfully submits that the amended Claims 1 to 11 in the Application are clearly allowable, and full reconsideration is requested.

If the Examiner has any questions or requires further information, he is respectfully requested to contact Applicants' Agent, Neil H. Hughes at (905) 771-6414 collect at his convenience.

Respectfully submitted,



Neil H. Hughes, P.Eng.  
Registration No. 33,636  
Agent for Applicant

NHH:mse  
Enclosures

- 20 -

S.N. 09/719,142  
Group Art Unit 1616

Amendment A

EXHIBIT ACLAIMS WITH MARKINGS TO SHOW CHANGES

1. (Amended) A pharmaceutical tablet comprising a shell in which is imbedded two smaller tablets covered by the material of the shell of the pharmaceutical tablet, one of which smaller tablets comprises an NSAID and the other of which smaller tablets comprises misoprostol, whereby the two smaller tablets are not exposed to the environment [of] at the surface of the pharmaceutical tablet, being protected by said shell.

- 21 -

S.N. 09/719,142  
Group Art Unit 1616

Amendment A

**EXHIBIT B**  
**CLEAN SET OF ALL PENDING CLAIMS**  
**FOLLOWING ENTRY OF THE PRESENT AMENDMENT**

1. A pharmaceutical tablet comprising a shell in which is imbedded two smaller tablets covered by the material of the shell of the pharmaceutical tablet, one of which smaller tablets comprises an NSAID and the other of which smaller tablets comprises misoprostol, whereby the two smaller tablets are not exposed to the environment at the surface of the pharmaceutical tablet, being protected by said shell.

2. The pharmaceutical tablet of Claim 1 wherein the smaller tablet containing the NSAID is enteric coated.

3. A pharmaceutical tablet as in Claim 1 or 2 wherein the NSAID is piroxicam.

4. A pharmaceutical tablet as in Claim 1 or 2 wherein the NSAID is selected from diclofenac and salts thereof.

5. A pharmaceutical tablet as in Claim 3 wherein the amount of piroxicam is from about 10 mg to about 20 mg.

6. A pharmaceutical tablet as in Claim 4 wherein the amount of diclofenac or a salt thereof is from about 25 mg to about 75 mg.

7. The pharmaceutical tablet of Claim 1 or 2 wherein the amount of misoprostol is about 200  $\mu$ g.

- 22 -

8. The pharmaceutical tablet of Claim 3 wherein the amount of misoprostol is about 200  $\mu\text{g}$ .
9. The pharmaceutical tablet of Claim 4 wherein the amount of misoprostol is about 200  $\mu\text{g}$ .
10. The pharmaceutical tablet of Claim 5 wherein the amount of misoprostol is about 200  $\mu\text{g}$ .
11. The pharmaceutical tablet of Claim 6 wherein the amount of misoprostol is about 200  $\mu\text{g}$ .

# Pharmaceutics: The Science of Dosage Form Design

---

EDITED BY

**Michael E. Aulton** BPharm PhD MPS  
Reader in Pharmacy, Leicester Polytechnic, Leicester, UK



---

EDINBURGH LONDON MELBOURNE AND NEW YORK 1988

37

*M P Summers*

## Granulation

### INTRODUCTION TO GRANULATION

#### Reasons for granulation

*To prevent segregation of the constituents in the powder mix*

*To improve the flow properties of the mix*

*To improve the compression characteristics of the mix*

*Other reasons*

#### Methods of granulation

*Dry granulation*

*Wet granulation (or wet massing)*

*Effect of granulation method on granule structure*

### PARTICLE BONDING MECHANISMS

*Adhesion and cohesion forces in immobile films*

*Interfacial forces in mobile liquid films*

*Solid bridges*

*Partial melting*

*Hardening binders*

*Crystallization of dissolved substances.*

*Attractive forces between solid particles*

### MECHANISMS OF GRANULE FORMATION

*Nucleation*

*Transition*

*Ball growth*

*Coalescence*

*Breakage*

*Abrasion transfer*

*Layering*

### PHARMACEUTICAL GRANULATION EQUIPMENT

*Wet granulators*

*Shear granulators*

*High speed mixer/granulators*

*Fluidized bed granulators*

*Spray driers*

*Spheronizers/pelletizers*

*Dry granulators*

*Sluggers*

*Roller compactors*

### INTRODUCTION TO GRANULATION

Granulation is the process in which powder particles are made to adhere to form larger particles called granules. In the majority of cases this will be undertaken in the production of tablets or capsules, when granules will be made as an intermediate product, but granules may also be used as a dosage form (see Chapter 17). Granulation will commence after mixing the necessary powdered ingredients so that a uniform distribution of each ingredient through the mix is achieved. After granulation, the granules will be packed when used as a dosage form or they may be mixed with other excipients prior to tablet compression or capsule filling.

#### Reasons for granulation

The reasons why granulation is often necessary are as follows.

*To prevent segregation of the constituents in the powder mix*

Segregation is primarily due to differences in the size or density of the components, the smaller particles concentrating at the base of a container with the large particles above them. An ideal granulation will contain all the constituents of the mix

## GRANULATION 617

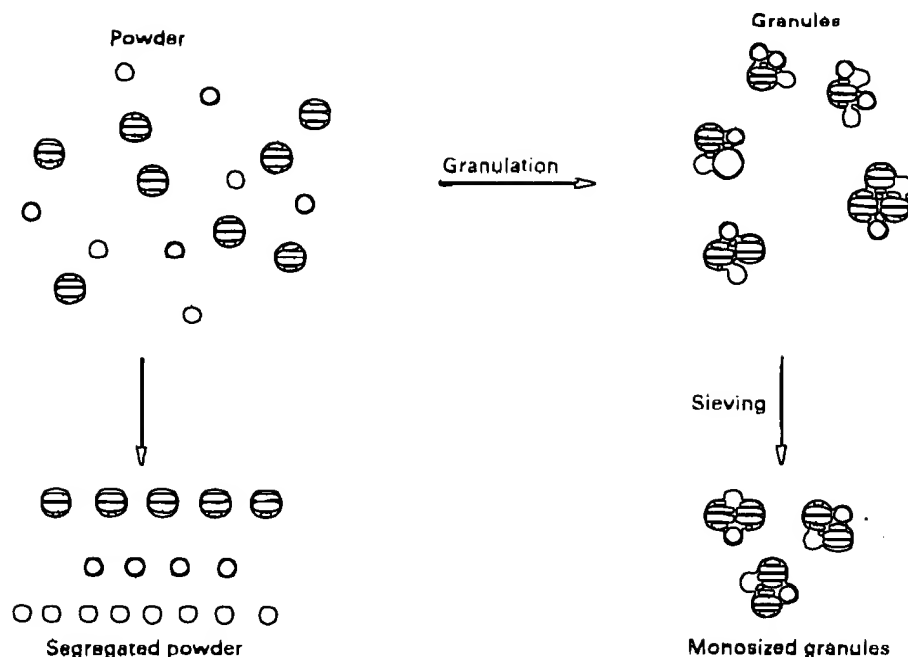


Fig. 37.1 Granulation to prevent powder segregation

in each granule and segregation of the ingredients will not occur (Fig. 37.1).

It is also important to control the particle size distribution of the granules because, although the individual components may not segregate, if there is a wide size distribution, the granules themselves may segregate. If this occurs in the hoppers of sachet filling machines, capsule filling machines or tablet machines, products having large weight variations will result. This is because these machines fill by volume rather than weight and if different regions in the hopper contain granules of different sizes (and hence bulk density), a given volume in each region will contain a different weight of granules. This will lead to an unacceptable distribution of the drug content within the batch of finished product even though the drug is evenly distributed weight per weight, through the granules.

#### *To improve the flow properties of the mix*

Many powders, because of their small size or surface characteristics, are cohesive and do not flow well. Poor flow will often result in a wide

weight variation within the final product due to variable fill of tablet dies, etc. Granules produced from such a cohesive system will be larger and more isodiametric, both factors contributing to improved flow properties.

#### *To improve the compression characteristics of the mix*

Some powders are difficult to compress even if a readily compressed adhesive is included in the mix but granules of the same formulation are often more easily compressed and produce stronger tablets. This is associated with the distribution of the adhesive within the granule and is a function of the method employed to produce the granule (Seager *et al.*, 1979).

#### *Other reasons*

These are the primary reasons for the granulation of pharmaceutical products but there are other reasons which may necessitate the granulation of powdered material:

- 1 The granulation of toxic materials will reduce

## 618 PHARMACEUTICAL TECHNOLOGY

the hazard of the generation of toxic dust which may arise when handling powders. Suitable precautions must be taken to ensure that such dust is not a hazard during the granulation process.

- 2 Materials which are slightly hygroscopic may adhere and form a cake if stored as a powder. Granulation may reduce this hazard as the granules will be able to absorb some moisture and yet retain their flowability because of their size.
- 3 Granules, being denser than the parent powder mix, occupy less volume per unit weight. They are therefore more convenient for storage or shipment.

### Methods of granulation

Granulation methods can be divided into two types: wet methods which utilize a liquid in the process and dry methods in which no liquid is used.

In a suitable formulation a number of different excipients will be needed in addition to the drug. The common types used are diluents, to produce a unit dose weight of suitable size and disintegrating agents which are added to disintegrate the granule in a liquid medium, e.g. on ingestion by the patient. Adhesives in the form of a dry powder may also be added, particularly if dry granulation is employed. These ingredients will be mixed before granulation.

### Dry granulation

In the dry methods of granulation the powder particles are aggregated using high pressure. There are two main processes. Either a large tablet (known as a 'slug') is produced in a heavy duty tableting press (a process known as 'slugging') or squeezed between two rollers to produce a sheet of material ('roller compaction'). In both cases these are broken using a suitable milling technique to produce granular material which is usually sieved to separate the desired size fraction. The unused fine material may be recycled to avoid waste. This dry method may be used for drugs which do not compress well after wet granulation or those which are sensitive to moisture.

### Wet granulation (or wet massing)

Wet granulation involves the massing of the powder mix using a solvent. The solvents used must be volatile, so that they can be removed by drying, and non-toxic. Typical solvents include water, ethanol and isopropanol either alone or in combination. The solvent may be used alone or it may contain a dissolved adhesive (also referred to as binder or binding agent) which is used to cause particle adhesion. The disadvantages of water as a solvent are that it may adversely affect drug stability, causing hydrolysis of susceptible products and it needs a longer drying time than organic solvents. This long drying time increases the length of the process and again may affect stability because of the extended exposure to heat. The primary advantage of water is that it is non-flammable which means that expensive safety precautions such as the use of flame-proof equipment need not be taken. Organic solvents are used when water-sensitive drugs are processed, as an alternative to dry granulation, or when a rapid drying time is required.

In the traditional wet granulation method the wet mass is forced through a sieve to produce wet granules which are then dried. A subsequent sieving stage breaks agglomerates of granules and removes the fine material which can be recycled. Variations of this traditional method are dependent upon the equipment used but the general principle of initial particle adhesion using a liquid remains in all of the processes.

### Effect of granulation method on granule structure

The type and capacity of granulating mixers significantly influences the work input and time necessary to produce a cohesive mass, adequate liquid distribution and intragranular porosity of the granular mass. The method and conditions of granulation affect intergranular and intragranular pore structure by changing the degree of packing within the granules. Seager *et al.* (1979) investigated the structure of granules prepared by various granulation methods. They showed that precompressed granules, consisting of compressed drug and binder particles, were held together by simple bonding during compaction. Granules



prepared by the wet massing consisted of intact drug particles held together in a sponge-like matrix of binder. Fluidized bed granules were similar to granules prepared by the wet massing process, but possessed greater porosity, and the granule surface was covered by a film of binding agent. With spray-dried systems, the granules consisted of spherical particles composed of an outer shell with an inner core of particles. This study graphically indicates that the properties of the granule are influenced by the manufacturing process.

### PARTICLE BONDING MECHANISMS

To form granules, bonds must be formed between powder particles so that they adhere and these bonds must be sufficiently strong to prevent breakdown of the granule to powder in subsequent handling operations.

Rumpf (1962) distinguished five primary bonding mechanisms between particles:

- 1 adhesion and cohesion forces in immobile liquid films,
- 2 interfacial forces in mobile liquid films,
- 3 solid bridges,
- 4 attractive forces between solid particles,
- 5 interlocking bonds.

Different types of mechanism were identified in each group and the ones discussed below are those which are of relevance to pharmaceutical granulations.

#### Adhesion and cohesion forces in immobile films

If sufficient liquid is present in a powder to form a very thin, immobile layer, there will be an effective decrease in interparticulate distance and increase in contact area between the particles. The bond strength between the particles will be increased because of this, as the van der Waals forces of attraction are proportional to the particle diameter and inversely proportional to the square of the distance of separation.

This situation will arise with adsorbed moisture and accounts for the cohesion of slightly damp

powders. Although such films may be present as residual liquid after granules prepared by wet granulation have been dried, it is unlikely that they contribute significantly to the final granule strength. In dry granulation, however, the pressures used will increase the contact area between the adsorption layers and decrease the interparticulate distance and this will contribute to the final granule strength.

Thin, immobile layers may also be formed by highly viscous solutions of adhesives and so the bond strength will be greater than that produced by the mobile films discussed below. The use of starch mucilage in pharmaceutical granulations may produce this type of film.

#### Interfacial forces in mobile liquid films

During wet granulation liquid is added to the powder mix and will be distributed as films around and between the particles. Sufficient liquid is usually added to exceed that necessary for an immobile layer and produce a mobile film. Newitt and Conway-Jones (1958) distinguished three states of water distribution between particles which are illustrated in Fig. 37.2.

At low moisture levels, termed the pendular state, the particles are held together by lens-

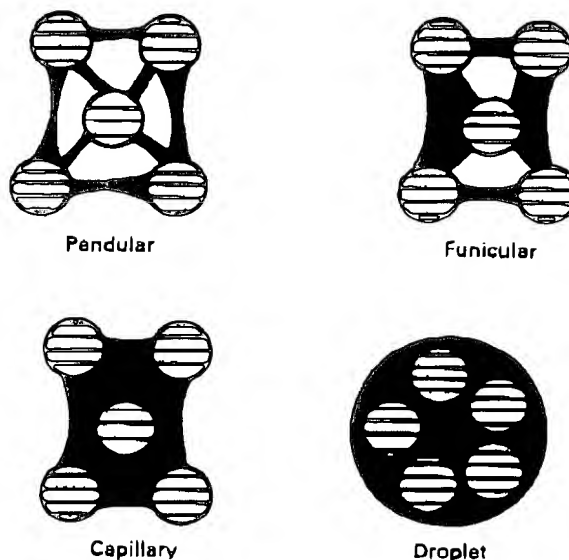


Fig. 37.2 Water distribution between particles

## 620 PHARMACEUTICAL TECHNOLOGY

shaped rings of liquid. These cause adhesion because of the surface tension forces of the liquid-air interface and the hydrostatic suction pressure in the liquid bridge. When all the air has been displaced from between the particles the capillary stage is reached and the particles are held by capillary suction at the liquid-air interface which is now only at the granule surface. The funicular state represents an intermediate stage between the pendular and capillary states. Moist-granule tensile strength increases about three times from the pendular to capillary state.

It may appear that the state of the powder bed is dependent upon the total moisture content of the wetted powders but the capillary state may also be reached by decreasing the separation of the particles. In the massing process during wet granulation, continued kneading/mixing of material originally in the pendular state will densify the wet mass, decreasing the pore volume occupied by air and eventually producing the funicular or capillary state without further liquid addition.

In addition to these three states, a further state, the droplet, is illustrated in Fig. 37.2. This will be important in the process of granulation by spray drying of a suspension. In this state, the strength of the droplet is dependent upon the surface tension of the liquid used.

These wet bridges are only temporary structures in wet granulation because the moist granules will be dried. They are, however, a prerequisite for the formation of solid bridges formed by adhesives present in the liquid or by materials which dissolve in the granulating liquid.

#### Solid bridges

These can be formed by:

- 1 partial melting,
- 2 hardening binders,
- 3 crystallization of dissolved substances.

#### Partial melting

Although not considered to be a predominant mechanism in pharmaceutical materials, it is possible that the pressures used in dry granulation methods may cause melting of low melting point

materials where the particles touch and high pressures are developed. When the pressure is relieved, crystallization will take place and bind the particles together.

#### Hardening binders

This is the common mechanism in pharmaceutical wet granulations when an adhesive is included in the granulating solvent. The liquid will form liquid bridges, as discussed above, and the adhesive will harden or crystallize on drying to form solid bridges to bind the particles. Adhesives such as polyvinylpyrrolidone, the cellulose derivatives (such as carboxymethylcellulose) and starch (added as a mucilage) all function in this way.

#### Crystallization of dissolved substances

The solvent used to mass the powder during wet granulation may dissolve one of the powdered ingredients. When the granules are dried, crystallization of this material will take place and the dissolved substance then acts as a hardening binder. Any material soluble in the granulating liquid will function in this manner; e.g. sucrose incorporated into dry powders granulated with water.

The size of the crystals produced in the bridge will be influenced by the rate of drying of the granules; the slower the drying time, the larger the particle size. It is therefore important that the drug does not dissolve in the granulating liquid and recrystallize because it may adversely affect the dissolution rate of the drug if crystals larger than that of the starting material are produced.

#### Attractive forces between solid particles

In the absence of liquids and solid bridges formed by binding agents, there are two types of attractive force which can operate between particles in pharmaceutical systems.

Electrostatic forces may be of importance in causing powder cohesion and the initial formation of agglomerates, e.g. during mixing. In general they do not contribute significantly to the final strength of the granule.

Van der Waals forces, however, are about four

orders of magnitude greater than electrostatic forces and contribute significantly to the strength of granules produced by dry granulation. The magnitude of these forces will increase as the distance between adjacent surfaces decreases and in dry granulation this is achieved using pressure to force the particles together.

## MECHANISMS OF GRANULE FORMATION

In the dry methods, adhesion of particles takes place because of applied pressure. A compact or sheet is produced which is larger than the granule size required and therefore the required size can be attained by milling and sieving.

In wet granulation methods, liquid added to dry powders has to be distributed through the powder by the mechanical agitation produced in the granulator. The particles adhere to each other because of liquid films and further agitation and/or liquid addition causes more particles to adhere. The precise mechanism by which a dry powder is transformed into a bed of granules is probably different for each type of granulation equipment but the mechanism discussed below, originally proposed for pan granulators, serves as a useful broad generalization of the process. The Freund granulator discussed later in this chapter utilizes a principle similar to that of a pan granulator and the mechanism will therefore be of direct relevance to granulation in this type of equipment.

The proposed granulation mechanism can be divided into three stages (Barlow, 1968):

### Nucleation

Granulation starts with particle-particle contact and adhesion due to liquid bridges. A number of particles will join to form the pendular state illustrated in Fig. 37.2. Further agitation densifies the pendular bodies to form the capillary state and these bodies act as nuclei for further granule growth.

### Transition

Nuclei can grow by two possible mechanisms: either single particles can be added to the nuclei

by pendular bridges or two or more nuclei may combine. The combined nuclei will be reshaped by the agitation of the bed.

This stage is characterized by the presence of a large number of small granules with a fairly wide size distribution. Providing that the size distribution is not excessively large, this point represents a suitable end-point for granules used in capsule and tablet manufacture as relatively small granules will produce a uniform tablet die or capsule fill. Larger granules may give rise to problems in small diameter dies due to bridging across the die and uneven fill.

### Ball growth

Further granule growth produces large, spherical granules and the mean particle size of the granulating system will increase with time. If agitation is continued, granule coalescence will continue and produce an unusable, overmassed system although this is dependent upon the amount of liquid added and the properties of the material being granulated.

Although ball growth produces granules which may be too large for pharmaceutical purposes, some degree of ball growth will occur in planetary mixers and it is an essential feature of some spheronizing equipment.

The four possible mechanisms of ball growth have been summarized by Sastry and Fuerstenau (1973) and are illustrated in Fig. 37.3.

### Coalescence

Two or more granules join to form a larger granule.

### Breakage

Granules break into fragments which adhere to other granules forming a layer of material over the surviving granule.

### Abrasion transfer

Agitation of the granule bed leads to attrition of material from granules. This abraded material adheres to other granules, increasing their size.

## 622 PHARMACEUTICAL TECHNOLOGY

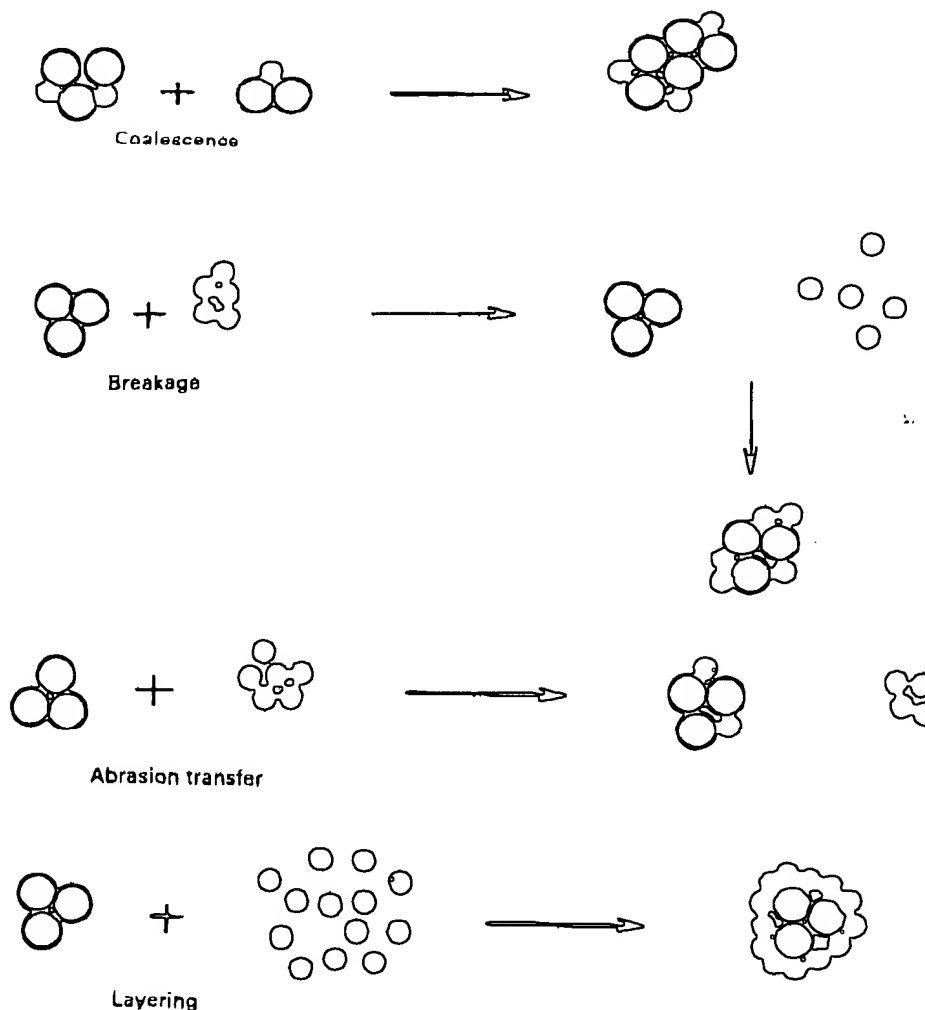


Fig. 37.3 Mechanisms of ball growth during granulation

*Layering*

When a second batch of powder mix is added to a bed of granules, the powder will adhere to the granules forming a layer over the surface increasing the granule size. This mechanism is only of relevance to the production of layered granules using spheronizing equipment.

There will be some degree of overlap between these stages and it will be very difficult to identify a given stage by inspection of the granulating system. For end-product uniformity it is desirable to finish every batch of a formulation at the same

stage and this may be a major problem in pharmaceutical production.

Using the slower processes such as the planetary mixer, there is usually a sufficient length of time to stop the process before overmassing. In faster granulation equipment, the duration of granulation can only be used as a control parameter when the formulation is such that granule growth is slow and takes place at a fairly uniform rate. In many cases, however, the transition from a non-granulated to an overmassed system is very rapid and monitoring equipment is necessary to stop the granulation at a predetermined point. Although

the topic of granulation end-point control is beyond the scope of this chapter, useful references are given in the bibliography.

## PHARMACEUTICAL GRANULATION EQUIPMENT

### Wet granulators

There are three main types of granulator used within the pharmaceutical industry for wet granulation.

#### *Shear granulators*

In the traditional granulation process a planetary mixer is often used for wet massing of the powders, e.g. Hobart, Collette, Beken (Fig. 37.4). Powder mixing usually has to be performed as a separate operation using suitable mixing equipment. With some formulations, such as those containing two or three ingredients in approximately equal quantities, however, it may be possible to achieve a suitable mix in the planetary mixer without a separate stage.

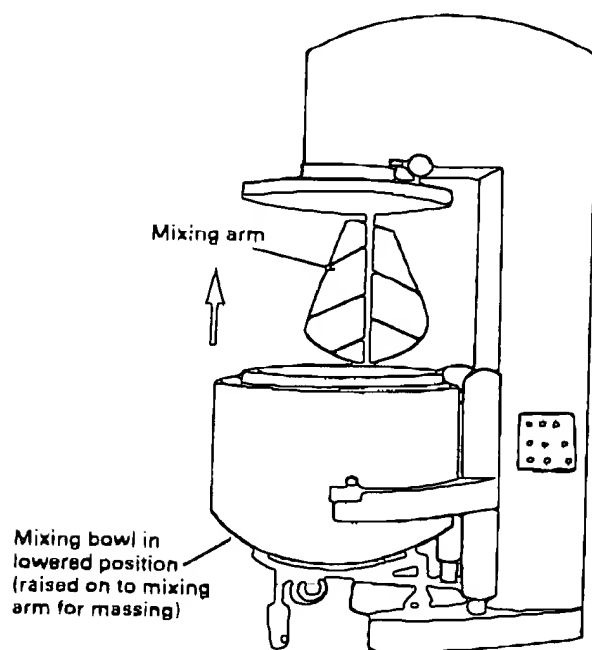


Fig. 37.4 Planetary mixer for wet massing

The mixed powders are fed into the bowl of the planetary mixer and granulating liquid added as the paddle of the mixer agitates the powders. The planetary action of the blade when mixing is similar to that of a household mixer.

The moist mass has then to be transferred to a granulator such as an oscillating granulator (Fig. 37.5). The rotor bars of the granulator oscillate and force the moist mass through the sieve screen, the size of which determines the granule size. The mass should be sufficiently moist to form discrete granules when sieved. If excess liquid is added, strings of material will be formed and if the mix is too dry the mass will be sieved to powder and granules will not be formed. The granules can be collected on trays and transferred to a drying oven although tray drying suffers from three major disadvantages:

- 1 There is a long drying time.
- 2 Migration of dissolved material to the upper surface of the bed of granules can take place as the solvent is only removed from the upper surface of the bed on the tray.
- 3 Granules may aggregate due to bridges formed at the points of contact of the granules.

To deaggregate the granules and remix them, a sieving stage is necessary after drying.

An alternative method is to dry the granules using a fluidized bed drier. This is a quicker method and as it keeps the individual granules separated during drying, it reduces the problems of aggregation and intergranular solute migration, reducing the need for a sieving stage after drying.

The disadvantages of this traditional granulation process are its long duration, the need for

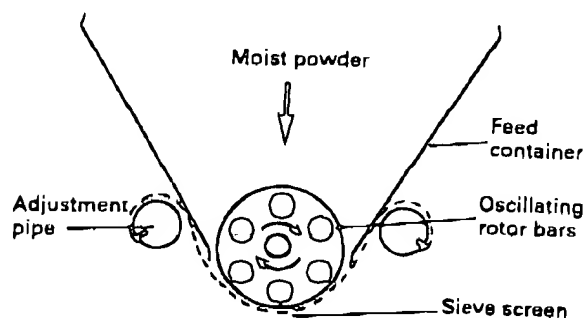


Fig. 37.5 Oscillating granulator

## 624 PHARMACEUTICAL TECHNOLOGY

several pieces of equipment and the high material losses which can be incurred because of the transfer stages. Advantages are that the process is not very sensitive to changes in the characteristics of the granule ingredients (e.g. surface area variations in different batches of an excipient) and the end-point of the massing process can often be determined by inspection.

*High speed mixer/granulators (e.g. Diosna, Fielder)*

This type of granulator was originally designed solely for mixing purposes but is now used extensively for granulation. The machines have a stainless steel mixing bowl containing a three-bladed impeller which revolves in the horizontal plane and a three-bladed auxiliary chopper which revolves in the vertical plane (Fig. 37.6).

The unmixed powders are placed in the bowl and mixed by the rotating impeller. Granulating liquid is then added via a port in the lid and this is mixed into the powders by the impeller. The chopper is usually switched on when the moist mass is formed because its function is to break up

the mass to produce a bed of fine, granular material. This granular product is usually sieved as it is being discharged into the bowl of a fluid bed drier simply to remove large aggregates.

The advantage of the process is that mixing, massing and granulation are all performed in a short period in the same piece of equipment. Granulation progresses so rapidly that a usable granule can be transformed very quickly into an unusable, overmassed system and it is often necessary to use a suitable monitoring system to indicate the end of the granulation process, i.e. when a granule of the desired properties has been attained. The process is also sensitive to variations in raw materials but this may be minimized by using a suitable end-point monitor.

A variation of the Diosna/Fielder design is the Collette-Gral mixer (Fig. 37.7). Based on the bowl and overhead drive of the planetary mixer, the single paddle is replaced with two mixing shafts. One of these carries three blades which rotate in the horizontal plane at the base of the bowl and the second carries smaller blades which act as the chopper and rotate in the horizontal plane in the upper regions of the granulating mass.

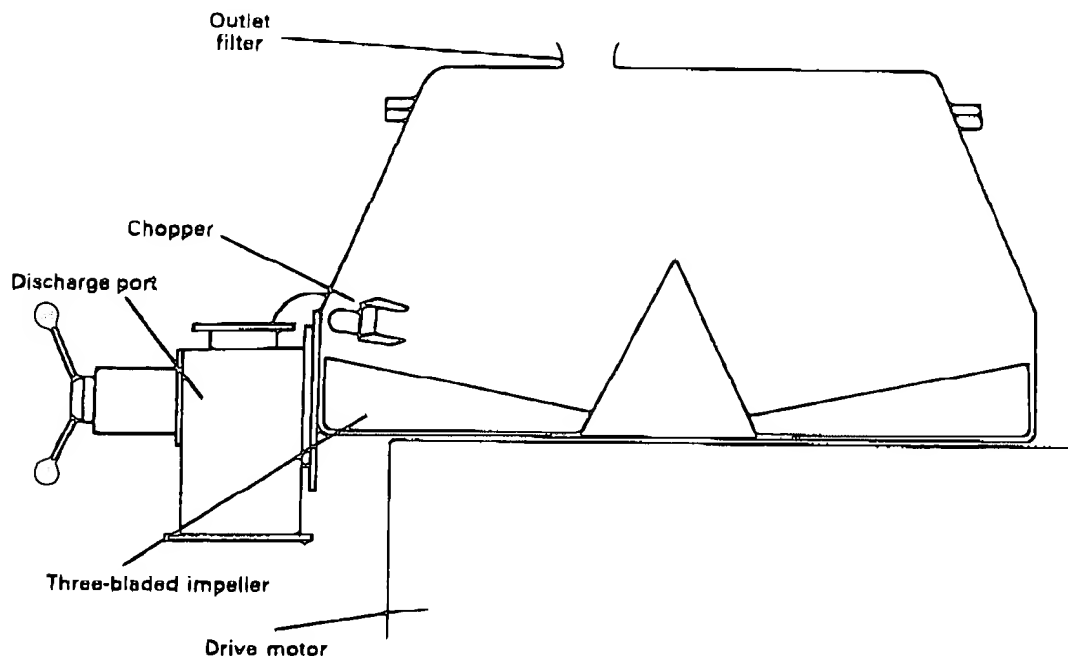


Fig. 37.6 High speed mixer/granulator

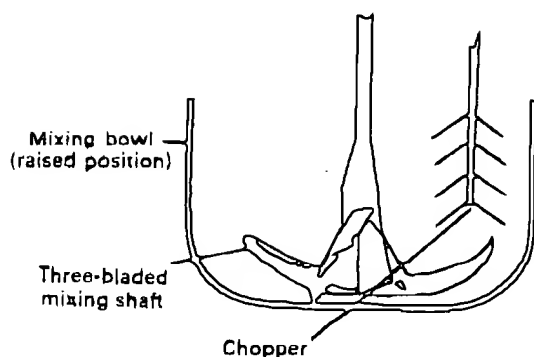


Fig. 37.7 Collette-Gral granulator: mixing shafts and bowl

*Fluidized bed granulators (e.g. Aeromatic, Glatt)*

The same principle utilized in fluidized bed drying, i.e. the fluidization of powder particles in a stream of air, is utilized for granulation in equipment of this type.

Heated air is blown or sucked through a bed of unmixed powders to fluidize the particles and mix the powders. Granulating liquid is pumped

through a spray nozzle over the particles and this liquid causes them to adhere when they collide. Escape of material from the granulation chamber is prevented by exhaust filters which are periodically agitated to reintroduce the collected material into the fluidized bed (Fig. 37.8). Sufficient liquid is added to produce granules of the required size which are then dried in the heated fluidizing air stream.

All the processes which normally need separate equipment in the traditional method are performed in one unit, saving labour costs, transfer losses and time although the equipment is initially expensive. Other advantages of the process are that units are available with in-line condensers for solvent recovery, the production of layered granules is possible and automation of the process can be achieved once the conditions affecting the granulation have been optimized.

The optimization of process (and product) parameters affecting granulation needs extensive development work not only during initial formulation work but also during scale-up from devel-

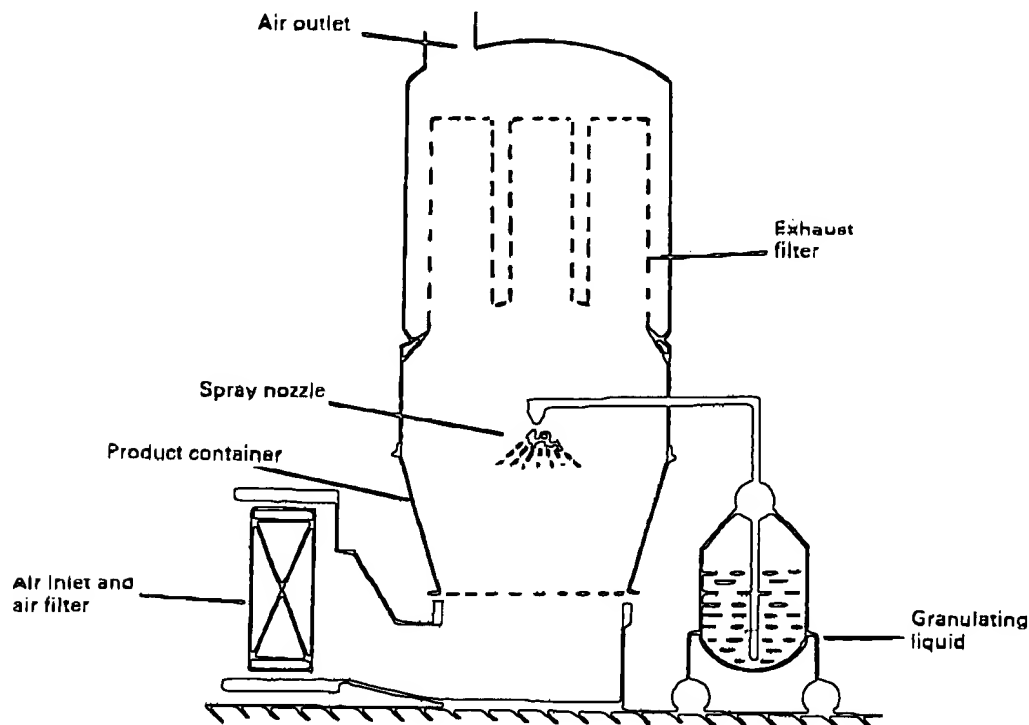


Fig. 37.8 Fluidized bed granulator

## 626 PHARMACEUTICAL TECHNOLOGY

opment to production scale. Similar development work for the traditional process and that using high-speed granulators is not as extensive. The parameters affecting the quality of the final granule include such variables as the adhesive concentration used in the granulating solution, the type of adhesive, the velocity and temperature of the fluidizing air and the air pressure used to atomize the granulating liquid. A useful summary of the effects of these variables is given by Aulton and Banks (1978).

The above are the three methods most commonly used in pharmaceutical processes but for more specialized applications other equipment can be utilized.

### Spray driers

A suspension of drug and excipients in adhesive solution can be dried in a spray drier (see Chapter 38). The resultant granules are free-flowing hollow spheres and the distribution of adhesive in such granules results in good compression properties (Seager *et al.*, 1979).

This process can be used to make tablet granules although it is probably economically justified for this purpose only when used almost continuously or when suitable granules cannot be produced by the other methods. The primary

advantages of the process are the short drying time and the minimal exposure of the product to heat due to the short residence time in the drying chamber. This means that little deterioration of heat-sensitive materials takes place and it may be the only process suitable for this type of product.

### Spheronizers/pelletizers

For some applications it may be desirable to have a dense, spherical pellet of the type difficult to produce with the equipment above, and spheronizing or pelletizing equipment is used, e.g. Caleva Spheroniser, Freund CF Granulator. Such pellets could be used, for example, for capsule filling when coated and non-coated drug-containing pellets would give some degree of programmed drug release after the capsule disintegrates.

In the Freund granulator, the powder mix is added to the bowl and wetted with granulating liquid (Fig. 37.9). The base plate rotates at high speed and centrifugal force keeps the moist mass at the edges of the rotor where the velocity difference between the rotor and static walls causes the mass to roll and break up, forming discrete spherical pellets. These are dried by the heated inlet air from the air chamber which also acts as a positive-pressure seal during granulation.

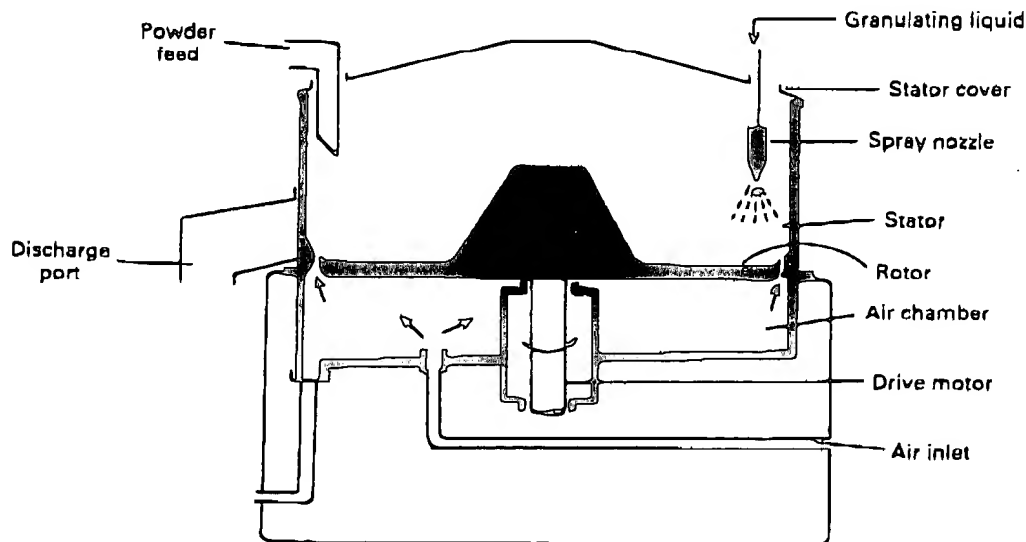


Fig. 37.9 Freund granulator



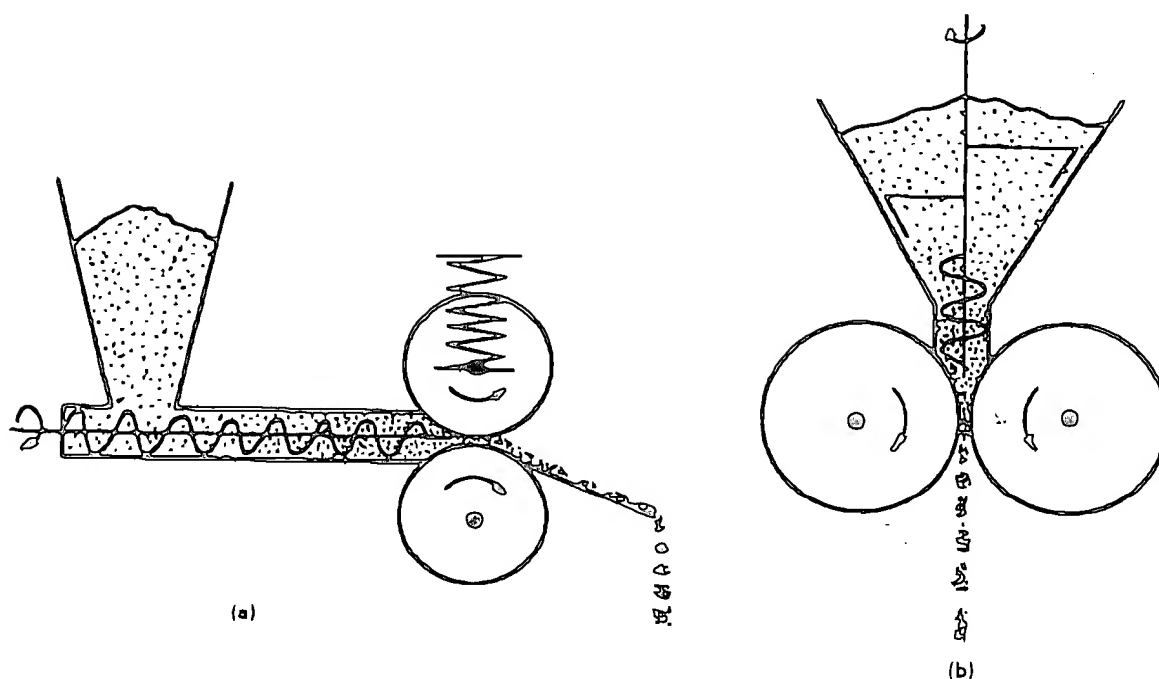


Fig. 37.10 Roller compaction: (a) Alexanderwerk and (b) Hutt types

Using this technique it is possible to coat the pellets by spraying coating solution on to the rotating pellets and layered pellets can be produced by using the pellets as nuclei in a second granulation with a powder mix of the coating ingredients.

The rotating base plate is a common feature of spheronizing equipment but some utilize a feed of pregranulated material which has been massed and extruded into short strings. Extrusion is a similar process to granulation in an oscillating granulator but requires a more moist mass than granulation processes and a more robust screen than that normally used in an oscillating granulator. For extrusion the wet mass can be fed through a perforated plate by an auger feed, a principle similar to that of the household mincer. The strings are fed on to a grooved or smooth rotating base plate and a velocity difference created by having static walls at the edge of the rotating plate breaks the material and rolls it into spheres. The spheres have then to be transferred to a fluidized bed drier for the drying process.

#### Dry granulators

The necessary pieces of equipment for dry granulation are first a machine for processing the dry powders and second a mill for breaking the compacts so produced.

#### Sluggers

The dry powders can be compressed using a tablet machine or, if higher pressures are required, a heavy duty rotary press can be used. This process is often known as 'slugging', the tablet made in the process being termed a 'slug'. See Chapter 39 for more details.

#### Roller compactors

Roller compaction is an alternative method, the powder mix being fed between rollers to form a compressed sheet (Fig. 37.10).

A hammer mill is suitable for breaking the compacts or sheets.

## 628 PHARMACEUTICAL TECHNOLOGY

## REFERENCES

- Aulton, M. and Banks, M. (1978) The factors affecting fluidised bed granulation. *Mfg Chem. Aerosol News*, 49, 50.
- Barlow, C. G. (1968) The granulation of powders. *The Chemical Engineer*, 220, CE196.
- Newitt, D. M. and Conway-Jones, J. M. (1958). A contribution to the theory and practice of granulation. *Trans. Inst. Chem. Engrs*, 36, 422.
- Rumpf, H. (1962) The strength of granules and agglomerates. In *Agglomeration* (ed. W. A. Knepper), p. 379, Interscience, New York.
- Sastry, K. V. S. and Fuerstenau, D. W. (1973) Mechanism of agglomerate growth in green pelletisation. *Powd. Tech.*, 7, 97.
- Seager, H., Burt, I., Ryder, J., Ruc, P., Murray, S., Beal, N. and Warrack, J. K. (1979) The relationship between granule structure, process of manufacture and the tableting properties of a granulated product. *Int. J. Pharm. Tech. Prod. Mfr.*, 1, 36.

## BIBLIOGRAPHY

## Granulation: mechanisms

- Capes, C. E. and Danckwerts, G. C. (1965) Granule formation by the agglomeration of damp powders. Part 1: The mechanism of granule growth. *Trans. Inst. Chem. Engrs*, 43, T116.
- Linkson, P. B., Glastonbury, J. R. and Duffy, G. J. (1973) The mechanism of granule growth in wet pelletising. *Trans. Inst. Chem. Engrs*, 51, 251.

## Granulation: equipment

- Gergely, G. (1981) Granulation — a new approach. *Mfg Chem. Aerosol News*, 52, 43.
- Strutt, B. (1976) New mixer/granulator. *Mfg Chem. Aerosol News*, 47, 47.

- Wood, R. (1975) Getting to grips with granulation. *Mfg Chem. Aerosol News*, 46, 23.

## Granulation: general

There are a large number of published papers and only a very limited number are listed below.

- Das, S. and Jarowski, C. I. (1979) Effect of granulating method on particle size distribution of granules and disintegrated tablets. *Drug Dev. Ind. Pharm.*, 5, 479.
- Doelker, E. and Shotton, E. (1977) The effect of some binding agents on the mechanical properties of granules and their compression characteristics. *J. Pharm. Pharmac.*, 29, 193.
- Ganderton, D. and Hunter, B. M. (1971) A comparison of granules prepared by pan granulation and massing and screening. *J. Pharm. Pharmac.*, 23 (Suppl), 1S.
- Hunter, B. M. and Ganderton, D. (1973) The influence on pharmaceutical granulation of the type and capacity of mixers. *J. Pharm. Pharmac.*, 25 (Suppl), 71P.
- Jaiyeoba, K. T. and Spring, M. S. (1980) The granulation of ternary mixtures: the effect of the solubility of the excipients. *J. Pharm. Pharmac.*, 32, 1.

## Granulation: end-point control

- Kay, D. and Record, P. C. (1978) Automatic wet granulation end-point control system. *Mfg Chem. Aerosol News*, 49, 45.
- Leuenberger, H., Bier, H. -P. and Sucker, H. (1979) Theory of the granulating-liquid requirement in the conventional granulation process. *Pharm. Tech. Int.*, 2, 35.
- Lindberg, N.-O. and Leander L. (1977) Studies on granulation in a small planetary mixer. *Acta Pharm. Suecica*, 14, 191, 197.
- Lindberg, N.-O. and Leander, L. (1982) Instrumentation of a Kenwood major domestic-type mixer for studies of granulation. *Drug Dev. Ind. Pharm.*, 8, 775.

# McGraw-Hill DICTIONARY OF SCIENTIFIC AND TECHNICAL TERMS

---

## Fourth Edition

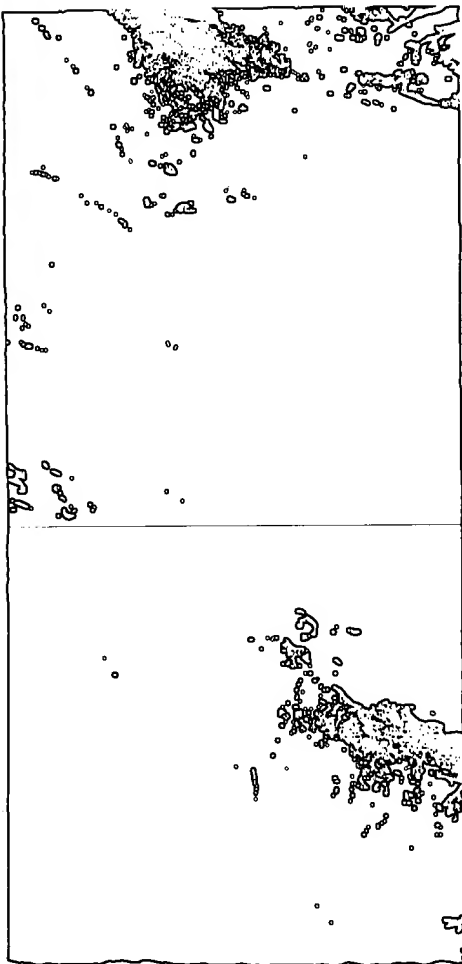
Sybil P. Parker

EDITOR IN CHIEF

**McGraw-Hill Book Company**

New York  
St. Louis  
San Francisco

Auckland	Bogotá
Caracas	Colorado Springs
Hamburg	Lisbon
London	Madrid
Mexico	Milan
Montreal	New Delhi
Oklahoma City	Panama
Paris	San Juan
São Paulo	Singapore
Sydney	Tokyo
Toronto	



## Grand Banks

## granulomatosis

823

side engages an inclined track at the dumping point. { 'gran-  
be, kār }

**Grand Banks** [GEOGR] Banks off southeastern Newfound-  
land, important for cod fishing. { 'grand, 'bānks }

**grand canonical ensemble** [STAT MECH] A collection of  
systems of particles used to describe an individual system which  
is allowed to exchange both energy and particles with its en-  
vironment. { 'grand kə'nān-ə-kel ən'sām-bəl }

**grandfather** [COMPUT SCI] A data set that is two generations  
earlier than the data set under consideration. { 'gran, fath-ər }

**grandfather cycle** [COMPUT SCI] The period during which  
records are kept but not used except to reconstruct other records  
which are accidentally lost. { 'gran, fath-ər, sī-kal }

**grandite** [MINERAL] A garnet that is intermediate in chemical  
composition between grossular and androite. { 'gran, dīt }

**grand mal** [MED] A complete epileptic seizure involving  
sudden loss of consciousness and tonic convulsion of the skele-  
tal musculature followed by clonic muscular spasms. { 'gran  
'māl }

**grandroll yarn** [TEXT] Yarn of blended or mixed colors  
made by twisting together two contrasting single yarns.  
{ 'gran'drel, 'yārn }

**grand unified field theory** [PARTIC PHYS] A theory in which  
the strong, electromagnetic, and weak interactions become as-  
pects of one interaction. { 'grand 'yū-nā, fīd 'fēld, thē-ərē }

**granellare** [INV ZOO] In xenophyophores, that portion of the  
body consisting of the multinucleate plasmodium and its en-  
closing, branching organic tube. { 'gran'al, ār }

**granite** [PETR] A visibly crystalline plutonic rock with gran-  
ular texture; composed of quartz and alkali feldspar with  
subordinate plagioclase and biotite and hornblende. { 'gran-  
ət }

**granite cloth** [TEXT] A fabric having a hard finish with an  
irregular pobbled surface made by weaving tightly twisted wool  
or blended yarns. { 'gran'ət, klōth }

**granite gneiss** [PETR] A banded metamorphic rock derived  
from igneous or sedimentary rocks mineralogically equivalent  
to granite. { 'gran'ət, nīs }

**granite moss** [BOT] The common name for a group of the  
class Bryatae represented by two Arctic genera and distin-  
guished by longitudinal splitting of the mature capsule into four  
valves. { 'gran'ət, mōs }

**granite pegmatite** See pegmatite. { 'gran'ət 'peg-mā, tīt }

**granite porphyry** See quartz porphyry. { 'gran'ət 'pōr-fē-rē }

**granite caries** [GEO] A sequence of products that evolve  
continuously during crustal fusion; earlier products tend to be  
deep-seated, syntectonic, and granodioritic, and later products  
tend to be shallower, late syntectonic, or postsyntectonic, and  
more potassic. { 'gran'ət, sī-rēz }

**granite wash** [GEO] Material eroded from granites and re-  
deposited, forming a rock with the same major mineral con-  
stituents as the original rock. { 'gran'ət, wāsh }

**granitic batholith** [GEO] A granitic shield mass intruded as  
the fusion of older formations. { 'grə'nīd-ik 'bath-ə, līth }

**granitic layer** See sial. { 'grə'nīd-ik 'lā-ər }

**granitic magma** [PETR] A coarse-grained igneous rock.  
{ 'grə'nīd-ik 'mag-mā }

**granitization** [PETR] A process whereby various types of  
rock may be converted to granite or closely related material.  
{ 'gran'əd-ə'zā-shən }

**granoblastic fabric** [PETR] The texture of metamorphic  
rocks composed of equidimensional elements formed during  
recrystallization. { 'grə'nō, blās-tīk 'fab-rīk }

**granodiorite** [PETR] A visibly crystalline plutonic rock com-  
posed chiefly of sodic plagioclase, alkali feldspar, quartz, and  
subordinate dark-colored minerals. { 'grə'nō'dī-ər, īt }

**granogabbro** [PETR] Plutonic rock composed of quartz,  
basic plagioclase, potash-feldspar, and at least one ferro-  
magnesian mineral; intermediate between a granite and a gabbro,  
and in a strict sense, a granodiorite with more than 50% boric  
plagioclase. { 'grə'nō'gā-brō }

**granophyre** [PETR] A quartz porphyry or fine-grained por-  
phyritic granite. { 'gran'ə, fīr }

**Graptolites** [INV ZOO] A family of calcareous sponges in the  
order Syctiida. { 'gran'tī-ə, dē }

**granular** [SCI TECH] Having a grainy texture. { 'gran-ya-  
lər }

**granular-bed separator** [ENG] Vessel or chamber in which  
a bed of granular material is used to remove dust from a dust-

laden gas as it passes through the bed. { 'gran-ya-lər, bed 'sep-  
ə, rād-ər }

**granular fracture** [MET] Grain-like or crystalline surface  
appearance of a broken metal. { 'gran-ya-lər 'frak-chər }

**granular gland** [ANAT] A gland that produces and secretes  
a granular material. { 'gran-ya-lər 'glānd }

**granular ice** [HYD] Ice composed of many tiny, opaque,  
white or milky pellets or grains frozen together and presenting  
a rough surface; this is the type of ice deposited as rime and  
compacted as névé. { 'gran-ya-lər 'īs }

**granularity** [GRAPHICS] The distribution of grains in a portion  
of photographic material that has been uniformly exposed and  
processed. { 'PETR } The feature of rock texture relating to the  
size of the constituent grains or crystals. { 'gran-ya-lər-əd-ē }

**granular leukocyte** See granulocyte. { 'gran-ya-lər 'lū-kə, sīt }

**granular powder** [MET] Equidimensional metal particles  
that are not spherical. { 'gran-ya-lər 'paūd-ər }

**granular snow** See snow grains. { 'gran-ya-lər 'sno }

**granular structure** [MATER] Nonuniform appearance of  
molded or compressed material due to presence of particles of  
composition, either within the material or on the surface.  
{ 'gran-ya-lər 'strak-chər }

**granulate** [CHEM] To form or crystallize into grains, gran-  
ules, or small masses. { 'gran-ya-lāt }

**granulated metal** [MET] Small pellets produced by pouring  
molten metal through a screen or similar device and chilling  
the droppings in water. { 'gran-ya-lād-əd 'med-əl }

**granulation** [ASTRON] The small "rice grain" markings on  
the sun's photosphere. Also known as photospheric granula-  
tion. [MED] 1. Tiny red granules made of capillary loops in  
the base of an ulcer. 2. Process of granular tissue formation  
around a focus of inflammation. [PL PATH] Dry, tasteless  
condition of citrus fruit due to hardening of the juice sacs when  
fruit is left on trees too late in the season. [SCI TECH] The  
state or process of reducing a material to grains or small par-  
ticles. { 'gran-ya-lā-shən }

**granulator** [FOOD ENG] A revolving cylinder in which sugar  
is dried and granulated. { 'gran-ya-lād-ər }

**granule** [ASTRON] A convective cell in the solar photo-  
sphere, about 600 miles (1000 kilometers) in diameter. [GEO] A  
somewhat rounded rock fragment ranging in diameter from  
2 to 4 millimeters; larger than a coarse sand grain and smaller  
than a pebble. { 'gran-yūl }

**granulite** [PETR] 1. Granite that contains muscovite. 2. A  
relatively coarse, granuloblastic rock formed at the high tem-  
peratures and pressures of the granulite facies. { 'gran-ya-līt }

**granulite facies** [PETR] A group of gneissic rocks charac-  
terized by a granuloblastic fabric and formed by regional dyna-  
mo thermal metamorphism at temperatures above 650°C and  
pressures of 3000-12,000 bars. { 'gran-ya-līt 'fā-shēz }

**granuloblastosis** [VET MED] An avian leukosis character-  
ized by the presence of excessive numbers of immature granu-  
locytes in the blood of affected birds. { 'gran-ya-lō, blā'stō-  
sās }

**granulocyte** [HISTOL] A leukocyte containing granules in  
the cytoplasm. Also known as granular leukocyte; polymorph;  
polymorphonuclear leukocyte. { 'gran-ya-lō, sīt }

**granulocytic leukemia** [MED] A blood disease involving  
neoplastic transformation of granulocytes, principally the neu-  
trophilic series. Also known as myelogenous leukemia; mye-  
loid leukemia. { 'gran-ya-lō, sīd-ik lū-kēm-ē-ə }

**granulocytopenia** [MED] A deficiency of granulocytes in  
circulating blood. Also known as granulopenia. { 'gran-ya-  
lō, sīd-ə'pēn-ya }

**granulocytosis** [MED] An increase in the number of granu-  
locytes in the circulation. { 'gran-ya-lō, sī'tō-sās }

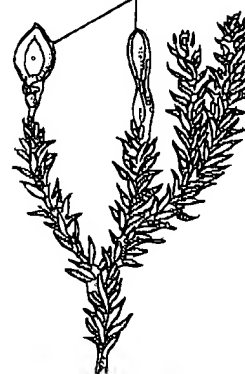
**granuloma** [MED] A discrete nodular lesion of inflammatory  
tissue in which granulation is significant. { 'gran-ya-lō-mā }

**granuloma inguinale** [MED] An infectious, chronic, de-  
structive granulomatous lesion of humans most frequently lo-  
calized in the genital and inguinal regions; caused by Donovan  
bodies (*Donovania granulomatis*). { 'gran-ya-lō-mā, īŋ-  
gwā'nālē }

**granuloma pyogenicum** [MED] A hemangioma with super-  
imposed inflammation on the skin or other epithelial surfaces.  
{ 'gran-ya-lō-mā, pī'ō-jen-ə-kəm }

**granulomatosis** [MED] Any disease characterized by mul-  
tiple granulomas. { 'gran-ya-lō-mā'tō-sās }

GRANITE MOSS  
sporophytes



Granite moss (*Andresia rupestris*),  
showing gametophyte with  
sporophytes. (From G. M. Smith,  
*Cryptogamic Botany*, vol. 2, 2d  
ed., McGraw-Hill, 1955)

# McGraw-Hill DICTIONARY OF SCIENTIFIC AND TECHNICAL TERMS

---

---

## Fourth Edition

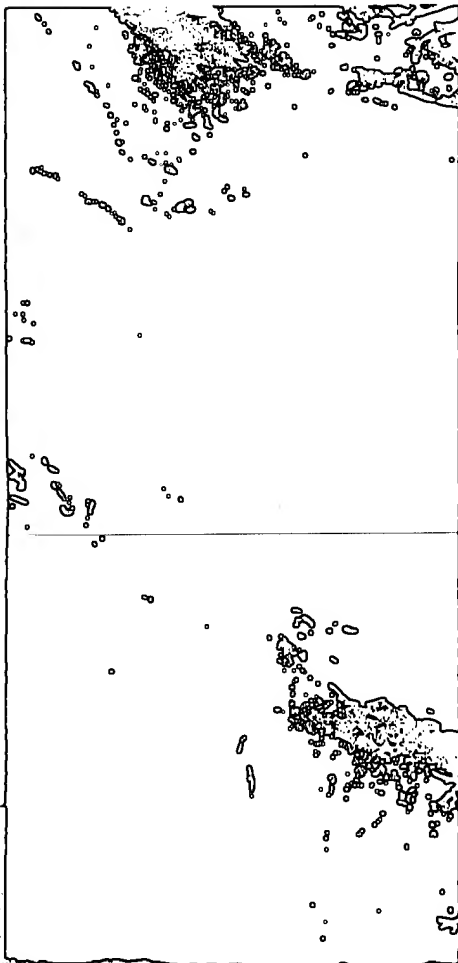
Sybil P. Parker

EDITOR IN CHIEF

McGraw-Hill Book Company

New York  
St. Louis  
San Francisco

Auckland	Bogotá
Caracas	Colorado Springs
Hamburg	Lisbon
London	Madrid
Mexico	Milan
Montreal	New Delhi
Oklahoma City	Panama
Paris	San Juan
São Paulo	Singapore
Sydney	Tokyo
Toronto	





1 See troy system.

T See tara; tesla.

2,4,5-T See 2,4,5-trichlorophenoxyacetic acid.

2,4,6-T See 2,4,6-trichlorophenol.

Ta See tantalum.

**Tabanidae** [INV ZOO] The deer and horse flies, a family of orthorrhaphous dipteran insects in the series Brachycera. { 'tā-bā'nā,de }

**tabbyite** [MINERAL] A variety of solid asphalt found in the western United States; used as rubber filler and with roofing materials. { 'tā-bē,īt }

**tab-card cutter** [DES ENG] A device for die-cutting card stock to uniform tabulating-card size. { 'tāb 'kād,kād-ər }

**Taber ice** See segregated ice. { 'tā-bər,īs }

**tabes dorsalis** [MED] A form of parenchymatous neurosyphilis in which there is demyelination and sclerosis of the posterior columns of the spinal cord. Also known as locomotor ataxia. { 'tā-bēz dōr'sā-lās }

**tabellae** See talik. { 'tā-bē-lā,ē,ēl }

**table** [COMPUT SCI] A set of contiguous, related items, each uniquely identified either by its relative position in the set or by some label. [LAP] The flat face forming the top of a brilliant-cut stone. [MATH] An array or listing of computed quantities. [MECH ENG] That part of a grinding machine which directly or indirectly supports the work being ground. [MIN ENG] 1. In placer mining, a wide, shallow sluice box designed to recover gold or other valuable material from screened gravel. 2. A platform or plate on which coal is screened and picked. { 'tā-bəl }

**table-driven compiler** [COMPUT SCI] A compiler in which the source language is described by a set of syntax rules. { 'tā-bəl 'driv-ən kəm'pī-lər }

**table-driven program** [COMPUT SCI] A computer program that relies on tables stored outside of the program in the computer's memory to furnish data. { 'tā-bəl 'driv-ən 'prō,gram }

**tabled whelk** [INV ZOO] *Neptunea tabulata*. A marine gastropod mollusk about 5 inches (13 centimeters) in length and 2 inches (5 centimeters) in diameter, found at depths of 150-200 feet (45-60 meters), off the west coast of Canada and the United States. { 'tā-bōld 'welk }

**table flotation** [MIN ENG] A flotation process in which a slurry of ore is fed to a shaking table where floatable particles become glomerules, held together by minute air bubbles and edge adhesion; the glomerules roll across the table and are discharged nearly opposite the feed end; the process is helped by jets of low-pressure air. { 'tā-bəl flō,tā'shən }

**table iceberg** See tabular iceberg. { 'tā-bəl 'īs,bərg }

**table knoll** [GEOGR] A knoll with a comparatively smooth, flat top. { 'tā-bəl 'nōl }

**tableland** [GEOGR] A broad, elevated, nearly level, and extensive region of land that has been deeply cut at intervals by valleys or broken by escarpments. Also known as continental plateau. { 'tā-bəl,ənd }

**table look-up** [COMPUT SCI] A procedure for calculating the location of an item in a table by means of an algorithm, rather than by conducting a search for the item. { 'tā-bəl 'lūk,əp }

**table look-up device** [ELECTR] A logic circuit in which the input signals are grouped as address digits to a memory device, and, in response to any particular combination of inputs, the memory device location that is addressed becomes the output. { 'tā-bəl 'lūk,əp dī,vīs }

**table management program** [COMPUT SCI] A computer program that handles the creation and maintenance of tables, and access to data stored in them. { 'tā-bəl 'mān-ij-mənt 'prō,gram }

**tablemount** See guyot. { 'tā-bəl,maunt }

**table mountain** [GEOGR] A flat-topped mountain. { 'tā-bəl,maunt-rən }

**table reef** [GEOG] A small, isolated organic reef which has a flat top and does not enclose a lagoon. { 'tā-bəl,rēf }

**table salt** See sodium chloride. { 'tā-bəl,sōlt }

**tablespoonful** [MECH] A unit of volume used particularly in cookery, equal to 4 fluid drams or ½ fluid ounce; in the United States this is equal to approximately 14.7868 cubic centimeters, in the United Kingdom to approximately 14.2065 cubic centimeters. Abbreviated tbsp. { 'tā-bəl'spūn,fūl }

**table sugar** See sucrose. { 'tā-bəl,shū,ər }

**tableting** [ENG] A punch-and-die procedure for the compaction of powdered or granular solids; used for pharmaceuticals, food products, fireworks, vitamins, and dyes. { 'tā-bəl-īŋ }

**tabling** [MIN ENG] Separation of two materials of different densities by passing a dilute suspension over a slightly inclined table having a reciprocal horizontal motion or shake with a slow forward motion and a fast return. { 'tā-b-līŋ }

**tab stop** [DES ENG] A column position to which the printing mechanism of a typewriter or computer printer advances upon receipt of a command. { 'tāb,stāp }

**tabula** [PALEON] A transverse septum that closes off the lower part of the polyp cavity in certain extinct corals and hydroids. { 'tā-byā-lā }

**tabular** [GEOG] Referring to a sedimentary particle whose length is two to three times its thickness. { 'tā-byā-lər }

**tabular berg** See tabular iceberg. { 'tā-byā-lər 'bərg }

**tabular crystal** [CRYSTAL] A crystal that appears broad and flat due to two prominent parallel faces. { 'tā-byā-lər 'krīst,əl }

**tabular iceberg** [OCEANOGR] An iceberg with clifflike sides and a flat top; usually arises by detachment from an ice shelf. Also known as table iceberg; tabular berg. { 'tā-byā-lər 'īs,bərg }

**tabular interpolation** [MATH] Method of finding from a table the values of the dependent variable for intermediate values of the independent variable. { 'tā-byā-lər in,tərpə'lā'shən }

**tabular language** [COMPUT SCI] A part of a program which represents the composition of a decision table required by the problem considered. { 'tā-byā-lər 'lāŋ,gwīj }

**tabular spar** See wollastonite. { 'tā-byā-lər 'spär }

**Tabulata** [PALEON] An extinct Paleozoic order of corals of the subclass Zoantharia characterized by an exclusively colonial mode of growth and by secretion of a calcareous exoskeleton of slender tubes. { 'tā-byā'lād-ā }

**tabulate** [COMPUT SCI] To order a set of data into a table form, or to print a set of data as a table, usually indicating differences and totals, or just totals. { 'tā-byā,lāt }

**tabulated altitude** [NAV] In navigational sight reduction tables, the altitude taken directly from a table for the entering arguments. { 'tā-byā,lād-əd 'āl-ti,tūd }

**tabulated azimuth** [NAV] Azimuth taken directly from a table, before interpolation. { 'tā-byā,lād-əd 'āz-əm-ēth }

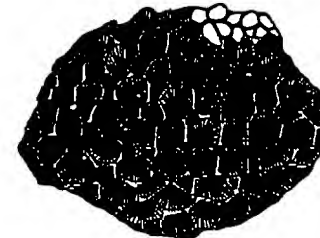
**tabulated azimuth angle** [NAV] Azimuth angle taken directly from a table, before interpolation. { 'tā-byā,lād-əd 'āz-əm-ēth,āŋ-gəl }

## TABLELAND



View of an ideal tableland: Canyon de Chelly National Monument, northeastern Arizona. (Spence Air Photos)

## TABULATA



Specimen of *Michelinia convexa* D'Orb, a representative species of the Tabulata, seen from above, from the Carboniferous Limestone of Ontario. (After Billings)